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EXAMINER	
STEELE, AMBER D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 09/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/659,083	DELAGRAVE, SIMON	
	Examiner	Art Unit	
	Amber D. Steele	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 April 2006 and 10 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *4,7 and 13-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5-6, and 8-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/20/06; 11/13/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1-50 are currently pending.

Claims 1-3, 5-6, and 8-12 are currently under consideration.

Election/Restrictions

2. Applicant's election with traverse of Group I (claims 1-12) in the reply filed on April 20, 2006 is acknowledged. The traversal is on the ground(s) that sufficient evidence showing that the groups are distinct has not been provided and that a serious search burden does not exist since all the groups are directed to aspects of in vitro coevolving. This is not found persuasive because while only two examples were provided in the March 22, 2006 Restriction requirement to show that the various methods had a materially different design other differences between the groups (methods and products) are also apparent (e.g. Group I requires coevolving a parent target and a parent neutralizing agent via diversifying; Group II requires coevolving a parent target and a parent neutralizing agent in order to generate a collection of evolved agents and targets, cross testing members of the collections, and identifying members of the collections; Group III requires diversifying in vitro a parent target and selecting a next generation target with new or improved resistance and diversifying in vitro a parent neutralizing agent and selecting a next generation neutralizing agent with new or improved neutralizing activity; Group IV requires diversifying and selecting a neutralizing agent and a parent target (in vivo possible); Group V requires contacting agent with target, selecting resistant targets, diversifying agents, contacting agents with resistant targets, selecting other agents, optionally repeating various steps; Group VI requires administering an agent to a patient; Group VII requires in vitro coevolving of antibodies

and targets to produce an antibody or target; Group VIII requires coevolving an antibody and a target to produce an antibody; Group IX is an antibody; Group X requires administering an antibody to a patient; Group XI requires coevolving an antigen and an agent; Group XII is an antigen; and Group XIII requires administering an antigen to a patient. In addition, the various groups all have different classification (e.g. class and/or subclass) and thus constitute a burdensome search.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 13-50 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on April 20, 2006.

4. Applicant's election of countering the development of resistance in a parent target to a parent neutralizing agent as the species of what the method is for, antigen as the species of parent target, protein as the species of neutralizing agent, desired neutralization profile as the species of outcome and mutagenesis as the species of diversifying in the replies filed on July 10, 2006 and April 20, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the election requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). It is noted that the election of both "countering the development of resistance in a parent target to a parent neutralizing agent" as the species of what the method is for and "desired neutralization profile" as the species of the outcome are

contradictory elections. Therefore, the examiner has taken into account both resistance and neutralizing activity in the search however claims based on neutralizing activity alone have been withdrawn from consideration since the applicants have elected countering resistance as the species of what the method is for.

5. Claims 4 and 7 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on July 10, 2006 and April 20, 2006.

Information Disclosure Statement

6. The information disclosure statement (IDS) submitted on April 20, 2006 and November 13, 2003 are being considered by the examiner.

Claim Objections

7. Claim 1 is objected to because of the following informalities: a nexus between the preamble and the last step of the method as presently claimed is missing (e.g. how does one counter the development of resistance via coevolving a parent target and a parent neutralizing agent). One of skill in the art would assume that all of the coevolved parent targets and parent neutralizing agents would not result in the countering of the development of resistance. Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-3, 5-6, and 8-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications under the 35 USC 112, first paragraph "Written Description" requirement, Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a **written description** rejection.

Claim 1 is drawn to a method for countering the development of resistance in a parent target to a parent neutralizing agent comprising coevolving a parent target and a parent neutralizing agent via diversifying the target and the neutralizing agent. The invention as claimed encompasses all known targets and neutralizing agents and all potential target and neutralizing agents since virtually any target can have an activity which can be partially neutralized or altered. The claimed invention states that coevolving comprises diversifying the parent target and the parent neutralizing agent in vitro. The claimed invention does not include any structural information regarding the target or the neutralizing agent. In addition, the claimed invention does not include any structural information regarding how a diversified target and neutralizing agent would counter the development of resistance.

The specification teaches that a "neutralizing agent" can be any entity capable of at least partially neutralizing at least one activity of a target and can be a cell, protein, nucleic acid, small molecule, virus, multicellular organism, or the like (please refer to paragraph 27) and the "target" is any entity having an activity that can be neutralized at least partially by a neutralizing agent

and can be a cell, protein, nucleic acid, small molecule, virus, multicellular organism, or the like (please refer to paragraph 30). In addition, the specification also teaches that "resistance" is anything that can thwart or withstand neutralizing activity (please refer to paragraph 31) and the method can utilize a receptor/ligand, target/neutralizing agent, pathogen/neutralizing agent, antigen/antibody, substrate/enzyme, ligand/ligand binding protein, drug/drug-binding molecule, nucleic acid/nucleic acid-binding protein, nucleic acid/nucleic acid-binding drug, nucleic acid/nucleic acid, phosphorylated protein/SH3 domain, or C-terminus of a polypeptide/PDZ domain (please refer to paragraph 23 and MPEP §2163.05 regarding "laundry lists"). However, the claimed invention does not include structural information regarding how coevolution of targets and neutralizing agents would counter the development of resistance (e.g. would every single cycle of coevolution or every single mutation of every target and every neutralizing agent produce targets and agents that would counter the development of resistance?). Furthermore, the specification does not teach how coevolving various targets and various neutralizing agents would counter the development of resistance for every potential cell, protein, nucleic acid, small molecule, virus, or multicellular organism or the extent of countering that is necessary to produce a tangible result. Therefore, one skilled in the relevant art would not reasonably conclude that the Applicants had possession of the invention as claimed since the structural limitations produced by the coevolution which would produce target and neutralizing agents that would counter resistance.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was *in possession of the invention.* The invention is, for purposes of the 'written description' inquiry,

whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See page 1116.).

With the exception of the monoclonal antibody-resistant mutants (MARMs) of respiratory syncytial virus (RSV) and neutralizing antibodies; vancomycin and vancomycin resistant Staphylococcus aureus; and STI-571 or Gleevec and chronic myeloid leukemia resistant to Gleevec as disclosed by the specification (see Examples 1-6), the skilled artisan cannot envision the method of claim 1. Furthermore, the examples do not provide information regarding the specific structural changes which resulted in resistance (e.g. potential target areas for coevolution) except those previously provided in the prior art (please refer to Table 1). Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class wherein the specification provided only the bovine sequence.

Therefore, the claims are extremely broad and encompass any known or unknown cell, protein, nucleic acid, small molecule, virus, or multicellular organism without any information regarding the mutations which arise that cause the development of resistance (e.g. starting point for coevolution which would counter resistance). In addition, the invention requires countering resistance to treatment, therapy, drugs, antibodies, small molecules, proteins, or nucleic acids without providing any information about how resistance forms in cells, viruses, or multicellular

organisms. Furthermore, the state of the prior art is varied with some means of resistance being well-characterized, some being linked to various mutations including multiple mutations, and others being unknown thus the level of predictability in the art is low in the broad sense of resistance and somewhat higher for known resistance mutations. However, the known resistance mutations do not provide information that can be extrapolated to other forms of resistance (e.g. multi-drug resistance is typically due to multiple mutations or incorporation of non-native genes) since resistance is dependent on the interaction of the drug, small molecule, protein, or nucleic acid with the target and the specific properties of the individual drug, small molecule, protein, or nucleic acid. The limited examples in the specification (please refer to Examples 1-6) do not provide adequate guidance to one of ordinary skill in the art in order to envision that the inventor had possession of each and every target and neutralizing agent that could counter the development of resistance in each and every known and unknown cell, virus, or multicellular organism. Please refer to the following reviews regarding the vast and unpredictable nature of the development of resistance and countering resistance: Stone, The Oncologist, 9: 259-270, 2004; Foster, The Journal of Clinical Investigation, 114(12): 1693-1696, 2004; Yoneyama et al., Biosci. Biotechnol. Biochem., 70(5): 1060-1075, 2006; Johnson et al., Topics in HIV Medicine, 13(1): 51-57, 2005; Cetinkaya et al., Clinical Microbiology Reviews, 13(4): 686-707, 2000; White et al., Clinical Microbiological Reviews, 11(2): 382-402, 1998; Cockerill, Antimicrobial Agents and Chemotherapy, 43(2): 199-212, 1999.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 1-3, 5-6, and 8-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Karrer et al. WO01/32712 A2 published May 10, 2001.

For present claim 1, Karrer et al. teach methods of improving antibodies via in vitro coevolution of an antibody and the cognate antigen wherein the antibody and/or antigen is selected for a desireable trait or property including increased affinity, decreased undesirable side-effects, increased avidity, etc. (please refer to abstract; pages 1-38 and 68-98; Tables 1, 2A, 2B).

For present claim 2, Karrer et al. teach mutagenesis (please refer to pages 17-34 and 70-89).

For present claim 3, Karrer et al. teach multiple rounds of diversification and selecting altered antibodies and/or antigens between the rounds of diversification (please refer to pages 6, 17, 28, 31, 82, 85-87).

For present claim 5, Karrer et al. teach improved neutralizing activity improved binding (e.g. improved countering of resistance; please refer to pages 6-8, 11-13, 17-20, 28, 31-32, 34-38, 68-73, 85-87).

For present claim 6, Karrer et al. teach repeating diversification until the desired outcome is obtained (please refer to pages 6, 17, 28, 31, 82, 85-87).

For present claim 8, Karrer et al. teach broad affinity and broad neutralizing activity (e.g. broad resistance; please refer to 6-8, 11-13, 17-20, 28, 31-32, 34-38, 68-73, 85-87).

For present claims 9-10, Karrer et al. teach antibodies as neutralizing agents (please refer to 6-8, 11-13, 17-20, 28, 31-32, 34-38, 68-73, 85-87).

For present claims 11-12, Karrer et al. teach antigens as targets (please refer to 6-8, 11-13, 17-20, 28, 31-32, 34-38, 68-73, 85-87).

Therefore, the presently claimed invention is anticipated by the teachings of Karrer et al.

12. Claims 1-3, 5-6, and 9-12 are rejected under 35 U.S.C. 102(e) as being anticipated by McCafferty et al. U.S. Patent 6,916,605 filed November 20, 1998.

For present claims 1-2, McCafferty et al. teach methods of mutation (e.g. diversifying) of members of specific binding pairs including antibodies and antigens in order to improve affinity (e.g. counter resistance; please refer to abstract; Figures 2A, 2B; columns 6-12, 14-18, 21-25; Examples 1-48).

For present claims 3 and 6, McCafferty et al. teach that the selection and mutagenesis can be repeated until the desired binding is achieved (please refer to columns 6-12, 14-18, 21-25; Examples 1-48).

For present claim 5, McCafferty et al. teach members of specific binding pairs with various binding affinities (please refer to columns 6-12, 14-18, 21-25; Examples 1-48).

For present claims 9-10, McCafferty et al. teach antibodies (please refer to columns 6-12, 14-18, 21-25; Examples 1-48).

For present claims 11-12, McCafferty et al. teach antigens (please refer to columns 6-12, 14-18, 21-25; Examples 1-48).

Therefore, the presently claimed invention is anticipated by the teachings of McCafferty et al.

Future Communications

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amber D. Steele whose telephone number is 571-272-5538. The examiner can normally be reached on Monday through Friday 9:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ADS
September 21, 2006

My-Chau Tran
Patent Examiner
AU1639